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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,553	11/20/2003	Hans Henrik Ipsen	04305/100E144-US2	3430
7278	7590	02/08/2007	EXAMINER	
DARBY & DARBY P.C. P. O. BOX 5257 NEW YORK, NY 10150-5257			ROONEY, NORA MAUREEN	
			ART UNIT	PAPER NUMBER
			1644	
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
3 MONTHS	02/08/2007	PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,553	IPSEN ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 November 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 36-96 is/are pending in the application.
- 4a) Of the above claim(s) 44-65 and 74-96 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 36-43 and 66-73 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 20 November 2003 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. 09/270,910.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>03/12/2004</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 36- 96 are pending.
2. Applicant's election without traverse of Group I, claims 36-43 and 66-73 and the 'Triple patch' mutant species of 'ix.' in claim 37, in the reply filed on 11/06/2006 is acknowledged.
3. Claims 44-65 and 74-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.
4. Claims 36-43 and 66-73 are currently under examination as they read upon a recombinant mutant Bet v 1 allergen and the 'Triple-patch' mutant of species of 'ix.' in claim 37.
5. The specification on page 1 should be amended to reflect the status of 09/270,910.
6. Applicant's IDS filed on 03/12/2004 is acknowledged.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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8. Claims 36-43 and 66-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 of copending Application No. 10/001,245. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner to be the same method of selection, or if not, by an obvious variant thereof. Specifically, Claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 teach a mutant Bet V1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical positions between the '245 application and the instant application, such as those recited in copending claim 22 and instant claim 37. Claim 22 of the '245 application recites substituting unspecified amino acids at one or more given positions, whereas the instant application recites specific substitutions at some of the same positions. However, on page 29 of the '245 specification in example 2595, the identical 'triple patch' mutant species of instant claim 37 is disclosed. Therefore, the claims are not patentably distinct from one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 36-43 and 66-73 are directed to the same invention as that of claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 of commonly assigned copending Application No. 10/001,245. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f)

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of this single invention must be resolved. Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly. Failure to comply with this requirement will result in a holding of abandonment of this application. It is noted that application 10/001,245 names four inventors, while the instant application names only three inventors.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 36, 38-43 and 66-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a recombinant mutant allergen from birch pollen major allergen Bet v a of SEQ ID NO:37 having the amino acid substitutions recited in claim 37.

However, applicant is not in possession of: a recombinant mutant Bet v 1 allergen derived from a naturally-occurring Bet v 1 allergen, said recombinant mutant Bet v 1 allergen having: (a) a substitution of a **solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates**, said substitution occurring in a **B-cell epitope of said naturally-occurring Bet v 1 allergen**; (b) reduced specific IgE binding compared to said naturally-occurring Bet v 1 allergen from which it is derived; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring Bet v 1 allergen** of claim 36; wherein said **solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 38; wherein **said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates** of claim 39; wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5% of claim 40; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1**

allergens is less than 2 Å in claim 41; wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen; wherein said solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally occurring Bet v 1 allergen occurs; or a recombinant mutant allergen derived from a naturally-occurring allergen selected from the group consisting of (i) allergens homologous to Bet v 1 allergen, said recombinant mutant allergens having:

(a) **a substitution of a solvent-accessible amino acid residue that is covered among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates, said substitution occurring in a B-cell epitope of said naturally-occurring allergen;** (b) reduced specific IgE binding compared to said naturally-occurring allergen; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring allergen of claim 66; wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37 of claim 67; wherein said solvent-accessible conserved amino acid residue has a solvent-accessibility of at least 20% of claim 68; wherein said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among**

homologous allergens within the taxonomic order from which said naturally-occurring allergen originates of claim 69; wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5% of claim 70; wherein **the average root mean square deviation of the atomic coordinates comparing the α -carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å** of claim 71; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å² of the surface of said naturally-occurring allergen** of claim 72; or wherein **said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs.**

The specification discloses recombinant mutant allergen from birch pollen major allergen comprising SEQ ID NO: 37 wherein said allergen has one or more amino acid substitutions such as the ones disclosed in claim 37. Other than the specific recombinant allergens recited in claim 37, there is inadequate written description of the structure and functions for any other recombinant allergen as set forth in claims 36, 38-43 and 66-73.

The disclosure does not provide adequate written support of the claimed genus of allergens for the following reasons: The guidelines for the Examination of Patent

Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri., January 5, 2001, see especially page 1106 column 3).

Because applicant only discloses the recombinant mutant allergen from birch pollen major allergen comprising SEQ ID NO: 37 wherein said allergen has one or more amino acid substitutions such as the ones disclosed in claim 37, there is a lack of a written description of any additional representative species of recombinant allergen, or recombinant mutant allergen.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently,

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Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 36, 38-43 and 66-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant mutant allergen from birch pollen major allergen Bet v 1 of SEQ ID NO:37 having the amino acid substitutions recited in claim 37, does not reasonably provide enablement for a recombinant mutant Bet v 1 allergen derived from a naturally-occurring Bet v 1 allergen, said recombinant mutant Bet v 1 allergen having: (a) a **substitution of a solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates**, said substitution occurring in a **B-cell epitope of said naturally-occurring Bet v 1 allergen**; (b) reduced specific IgE binding compared to said naturally-occurring Bet v 1 allergen from which it is derived; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring Bet v 1 allergen** of claim 36; wherein said **solvent accessible conserved amino acid residue has a solvent accessibility of at least 20% of claim 38**; wherein said **conserved solvent-accessible amino acid residue is conserved**

with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates of claim 39; wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5% of claim 40; wherein the average root mean square deviation of the atomic coordinates comparing the α -carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å in claim 41; wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen of claim 42; wherein said solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally occurring Bet v 1 allergen occurs of claim 43; or a recombinant mutant allergen derived from a naturally-occurring allergen selected from the group consisting of (i) allergens homologous to Bet v 1 allergen, said recombinant mutant allergens having: (a) a substitution of a solvent-accessible amino acid residue that is covered among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates, said substitution occurring in a B-cell epitope of said naturally-occurring allergen; (b) reduced specific IgE binding compared to said naturally-occurring allergen; and (c) an α -carbon backbone tertiary

structure that is preserved as compared to the α -carbon backbone tertiary structure of said naturally-occurring allergen of claim 66; wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37 of claim 67; wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20% of claim 68; wherein said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates of claim 69; wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5% of claim 70; wherein the average root mean square deviation of the atomic coordinates comparing the α -carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 \AA of claim 71; wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 \AA^2 of the surface of said naturally-occurring allergen of claim 72; or wherein said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen is substituted with an amino acid that is not conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs of claim 73.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only the recombinant mutant allergen from birch pollen major allergen comprising SEQ ID NO: 37 wherein said allergen has one or more amino acid substitutions such as the ones recited in claim 37. Other than the specific amino acid substitutions in the Bet v 1 allergen of SEQ ID NO: 37 mentioned above, the specification does not teach how to make and use any other recombinant mutant Bet v 1 allergen in which: at least one solvent-accessible amino acid residue of any B cell epitope at any position which is conserved in the amino acid sequences of Bet v 1 homologous allergens within the taxonomic order from which the naturally occurring Bet v 1 allergen originates is substituted with any amino acid residue, specific IgE binding to

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the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen; and the recombinant mutant allergen has an α -carbon backbone tertiary structure essentially the same as the α -carbon backbone tertiary structure of the naturally occurring allergen.

There is also insufficient guidance in the working examples of allergen mutants wherein: the solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%; the conserved solvent-accessible amino acid residue is conserved with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates; the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%; the average root mean square deviation of the atomic coordinates comparing the α -carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 \AA ; conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 \AA of the surface of said naturally-occurring Bet v 1 allergen; the allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37; or wherein said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen is substituted with an

amino acid that is not conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs.

Claim 36 recites comparing homologous proteins to select the identity of the amino acid residues to be substituted at a position chosen for mutagenesis. It is noted that the specification defines substitution as comprising deletions and additions of single amino acids as well as single amino acid substitutions, but given that the claim recites "substitution of one surface-exposed amino acid residue with another residue" the mutant allergens do not comprise additions or deletions since an addition comprises two residues and a deletion does not comprise any residue. The specification does not define a particular algorithm to be used in determining homology and it is known in the art that parameters such as gap length, substitution matrices, and percent cutoffs influence homology calculations (The Statistics of Sequence Similarity Scores downloaded from [ncbi.nlm.nih.gov BLASTtutorial/Altschul-I.html](http://ncbi.nlm.nih.gov/BLAST/tutorial/Altschul-I.html), PTO-892, Page 1, Reference U, see entire document). Calculations made with different parameters will identify different sets of homologous proteins and thus change the amino acids possible for substitution. Also, in order to compare the homology of the naturally occurring Bet v 1 allergens, all Bet v 1 allergens must be known prior to generating the mutant allergens. The scope of the independent claim reads on all naturally occurring Bet v 1 allergens, including those presently unidentified by scientists. The structures of all Bet v 1 allergens are not known, and crystallization of proteins for structure determination is

unpredictable and is based upon trial and error (Kundrot et al., PTO-892, Reference V, see entire document and abstract).

There is insufficient guidance and working example as to which amino acid residues within the B cell epitope of any Bet v 1 allergen within the taxonomic order that can be substituted and still retain the a-carbon backbone tertiary structure and reduced IgE binding as compared to the naturally occurring allergen. It is well known in the art that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (Ngo et al., PTO-892, page 1, Reference W). The state of the prior art is shows that determining the IgE binding of the Bet v 1 B cell epitope is dependent upon protein conformational structure (Lebecque et al., Page 1, PTO-892, Reference X; Gajhede et al., PTO-892, Page 2 Reference U; and Elsayed et al., PTO-892 Page 2, Reference V). Given the diversity of B cell epitopes ranging from conformational to linear epitope structures, there is no predictability regarding what effect amino acid substitutions will have on the structure and function of all allergens to which the antibody binds because it is difficult to predict the 3-D structure of modified allergens from a primary structure such as amino acid sequence alignment.

Given the insufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of any allergen mentioned above that, after substitution, will retain both structure and reduce IgE binding is unpredictable. Since the

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specification fails to provide guidance regarding which amino acids can tolerate change, it follows that any allergen other than the Bet v 1 mutants mentioned above are not enabled.

One of ordinary skill in the art could not predict which undisclosed amino acid or amino acids within the full length amino acid sequence of any Bet v 1 allergen could be substituted for which amino acid and whether the resulting recombinant allergen exhibits reduced IgE binding while maintaining the overall α -carbon backbone tertiary structure. Predicting polypeptide structure from sequence data of a single amino acid sequence and attempting to utilize the predicted structural determinations to ascertain IgE binding or functional aspects of any Bet v 1 allergen and what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. *In re Fisher* indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Complex procedures such as X-ray crystallography and NMR spectroscopy require highly skill in the art to perform. It is outside the realm of routine experimentation to perform X-ray crystallography or NMR for any naturally occurring Bet v 1 allergen. In the instant application, it is noted that various mutations, substitutions and the like provide a range of activities and not all which are necessarily predictive of reduced IgE binding while the overall α -carbon backbone tertiary structure is preserved (See Figure 7). It was well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related

compounds or compositions could result in substantially different pharmacological activities.

Other than recombinant mutant allergen from birch pollen major allergen Bet v 1 of SEQ ID NO:37 having one or more amino acid substitutions such as the ones recited in claim 37, there is insufficient guidance as to which amino acid residues within which B cell epitope of the full-length amino acid sequence of any Bet v 1 allergen can be changed and to which amino acid residues to result in a recombinant allergen with reduced IgE binding. The lack of sufficient guidance and predictability in determining which modifications would lead to reduced IgE binding while the overall α -carbon backbone tertiary structure is preserved and the relationship between the amino acid sequence of an allergen and its tertiary structure (Ngo et al., PTO-892, Page 1, Reference W), it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed invention. Blumenthal et al. teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (PTO-892, Page 2, Reference W, see entire document and page 39 of third full paragraph). Skolnick et al. teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure, i.e., amino acid sequence, does not necessary tell one its function (PTO-892, Page 2, Reference X, entire document and abstract). Attwood et al. teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure

prediction methods is unreliable (PTO-892, Page 3, Reference U, entire document).

Given the lack of guidance as to which specific amino acid within the B cell epitope of any known or unknown naturally occurring Bet v 1 allergen can tolerate change, it is unpredictable which recombinant mutant allergen would reduce binding of IgE by at least 5% while the alpha-carbon backbone is preserved.

Therefore, based upon the breadth of applicant's claimed invention, the unpredictability concerning the identity of all naturally occurring Bet v 1 allergens, the generation of crystallographic data concerning said allergens, the correlation between IgE binding and allergen structure, the identification of amino acid residues suitable for substitution based upon homology, and the inability determine which substitutions would satisfy dependent claims 38-43 and 67-73, a skilled artisan would be unable to make and use the full breadth of applicant's claimed invention without conducting undue research.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

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13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

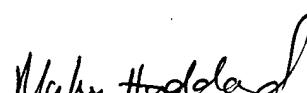
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 2, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600



MAHER M. HADDAD
PRIMARY EXAMINER